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MORPHOMETRIC VARIABILITY OF THE HUMAN UPPER BRONCHIAL TREE

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Abstract. Available morphometric models of the human tracheobronchial tree are based on measurements of a small number of individuals from a few laboratories. In order to determine the degree of intersubject variability, and its relationship to intrasubject variability, analysis of airway lengths, diameters and branching angles was performed using solid casts of the upper bronchial trees from a series of human lungs. The results indicate that there are significant differences between subjects. Inter- and intrasubject variabilities should be considered in occupational and environmental hazard evaluation, and when extrapolating and modeling inhalation toxicologic data.

Airway Human Morphometry
Bronchus Lung Trachea

Morphometric measurements of the human bronchial airways and models describing their structure have been reported by a number of investigators (*e.g.*, Davies, 1961; Findeisen, 1935; Horsfield *et al.*, 1971; Landahl, 1950; Olson *et al.*, 1970; Weibel, 1963; Yeh and Schum, 1980). These studies have been performed for descriptive quantitative geometry, as well as for use in the calculation of parameters such as pressure drop and flow velocities during breathing (Olson *et al.*, 1970; Sekihara *et al.*, 1968). In addition, morphometric measurements have been incorporated into aerosol deposition models used for evaluation of hazards due to inhaled environmental and occupational particulate matter (Beeckmans, 1965a,b; Chan *et al.*, 1980; Cheng and Yeh, 1981; Davies, 1972, 1980; Findeisen, 1935; Martonen, 1983; Task Group on Lung Dynamics, 1966; Taulbee and Yu, 1975; Yu, 1978) and for the interpretation of results from inhalation toxicology studies.

Positive solid casts prepared from human lungs have been used in a number of studies for the measurement of bronchial airway dimensions (Horsfield *et al.*, 1971; Olson *et al.*, 1970; Schlesinger *et al.*, 1977; Weibel, 1963; Yeh and Schum, 1980). However, in each

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of these cases, a cast prepared from a single individual was the sole source of the anatomic data, although each of the casts was reportedly from an 'average' lung. The actual degree of intersubject variability is not clear, since data obtained by these various investigators are not directly comparable due to differences in methods of cast preparation and measurement, and in airway ordering schemes. To date, the only attempt to estimate the inter- and intrasubject variability of lung geometry has been a statistical description based upon Weibel's Model A performed by Soong *et al.* (1979). While this approach has its merits, actual measurements of several tracheobronchial trees in one laboratory are needed in order to determine the degree of variability between individuals. This paper describes morphometric measurements obtained from eight casts of the upper bronchial tree prepared from adult right lungs.

Materials and methods

Preparation of the lungs. Four pairs and four single right lungs of male, sudden death accident victims were obtained at autopsy from the Office of the New York City Chief Medical Examiner; no gross abnormalities or pathology were observed. The characteristics of the study group were as follows: median age = 27.5 years (range = 17–45 years); median height = 178.1 cm (range = 171.4–188.0 cm). The lungs were initially prepared by gently suctioning excess mucus from the trachea or right main bronchus. Any small leaks were repaired by application of Krazy Glue® (Itasca, IL). The lungs were perfused with isotonic saline through the pulmonary vasculature, and allowed to drain overnight while refrigerated. They were then inflated to 25 cm H_2O by positive air pressure through the trachea or main bronchus while suspended in a freeze-drying apparatus (Virtis Co., Gardiner, NY). Complete freeze drying of the lungs took about five days.

Production of the solid cast. Casts were prepared using an RTV silicone-rubber molding compound, as described by Schlesinger *et al.* (1982). After 24–48 h curing time, the total volume of the lung was determined by water displacement. From this, the air volume of the fixed lung was calculated, and compared to the predicted *in vivo* total lung capacity (TLC) (Cotes, 1979); the average percentage of predicted for the eight subjects was found to be 67%.

To remove the tissue, the lung was placed in a 16 M NaOH bath, and frequently rinsed with water, until the cast was completely exposed.

Morphometric measurements. Measurements of length, diameter and branching angle were made from the level of the main bronchus through the eighth branching level beyond the trachea, using the method of Raabe *et al.* (1976). Since the casts were complete through the sixth generation, all airways through this level were measured; however, in one cast, the entire main bronchus (generation 1) was not attached and thus could not be measured. All available airways of generations 7 and 8 were measured;

these represented 73% and 38%, respectively, of the total number which was predicted assuming dichotomous branching, although trichotomous branching was occasionally found in some of the casts at various levels. Eighth generation measurements in one cast were not included at all, since a sufficient number of these airways were not present to provide a statistically representative sample. The airway identification system of Phalen *et al.* (1978) was used to indicate the position of the airways relative to each other and to the trachea.

Lengths and midpoint diameters were measured with an electronic digital caliper accurate to 0.01 mm. Branching angles were measured to the nearest 5° with a hand-held magnifier incorporating a 360° protractor reticule.

Data analysis The data were tabulated, sorted, and statistical tests performed using the Minitab™ computer program (Minitab Project, University Park, PA). Unless noted otherwise, the significance level chosen was $P \leqslant 0.05$.

Results

The mean lengths (l) and diameters (d) of the eight casts are shown *vs* generation number (z) in fig. 1. It is apparent that there is more intersubject variability in length than in diameter. Although both the mean diameters and lengths are log-normally distributed by generation, the fit for the latter is poorer. The regression equations describing the diameter *vs* generation and length *vs* generation relationships are $d_z = d_1$

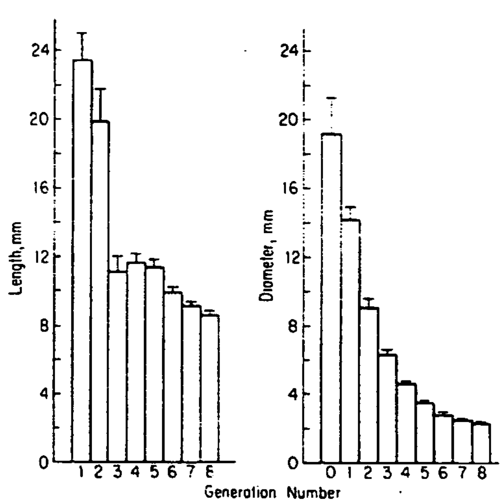

Fig. 1. Left: Airway length (mean ± SEM) *vs* generation. Right: Airway diameter (mean ± SEM) *vs* generation.

TABLE 1
Diameter and length parameters by generation of eight casts

Generation	n	Diameters (mm)				Lengths (mm)			
		$\bar{X}$[a]	SD[b]	Gm[c]	σ_g[d]	$\bar{X}$[a]	SD[b]	Gm[c]	σ_g[d]
1[e]	7	14.21	1.93	14.10	1.14	23.43	4.42	23.07	1.21
2	16	9.10	2.05	8.89	1.25	19.83	7.78	18.33	1.52
3	34	6.31	2.09	6.03	1.34	11.13	5.01	10.00	1.62
4	69	4.59	1.44	4.40	1.33	11.64	4.35	10.86	1.47
5	142	3.55	1.26	3.36	1.38	11.38	4.82	10.43	1.53
6	262	2.80	0.97	2.66	1.37	9.90	5.37	8.71	1.66
7	374	2.47	0.88	2.33	1.39	9.14	4.73	8.12	1.62
8[e]	344	2.26	0.87	2.11	1.44	8.64	4.33	7.70	1.62

[a] Arithmetic mean.
[b] Standard deviation.
[c] Geometric mean.
[d] Geometric standard deviation.
[e] n = 7.

$[2.70^{-0.27z}]$, ($r^2 = 0.95$) and $l_z = l_1 [3.08^{-0.145z}]$; ($r^2 = 0.78$), respectively. It should be noted that the distributions of individual length and diameter measurements within each generation were also log-normal (table 1). The geometric standard deviations are low, however, indicating populations only slightly skewed from a normal distribution. Since the calculated geometric means differed from the arithmetic means by $\leqslant 12\%$ and since other investigators have described their data in terms of arithmetic means, the data presented here are described in that same manner for consistency.

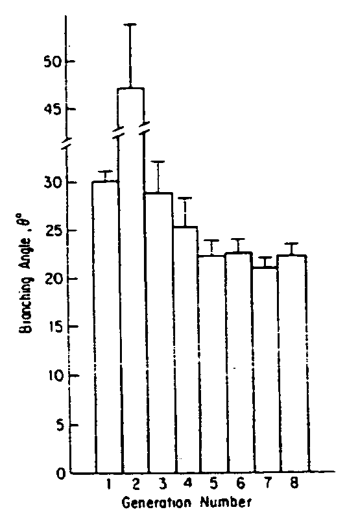

Fig. 2. Airway branching angle (mean ± SEM) *vs* generation.

The intersubject range of branching angles is wider than that for lengths and diameters (fig. 2). Beginning with generation 5, however, the angles become quite uniform, with mean values between 20° and 25°.

Figure 3a presents values for the mean length to diameter ratio ($\overline{l/d}$) *vs* airway generation. It can be seen that this ratio changes abruptly between the 4th and 5th branching generations. The rate of change is constant for generations 5–8, while for generations 1 to 4 there is no linear relationship at all.

Figure 3b shows $\overline{l/d}$ *vs* airway diameter interval (d_i). Here it is seen that the $\overline{l/d}$ values

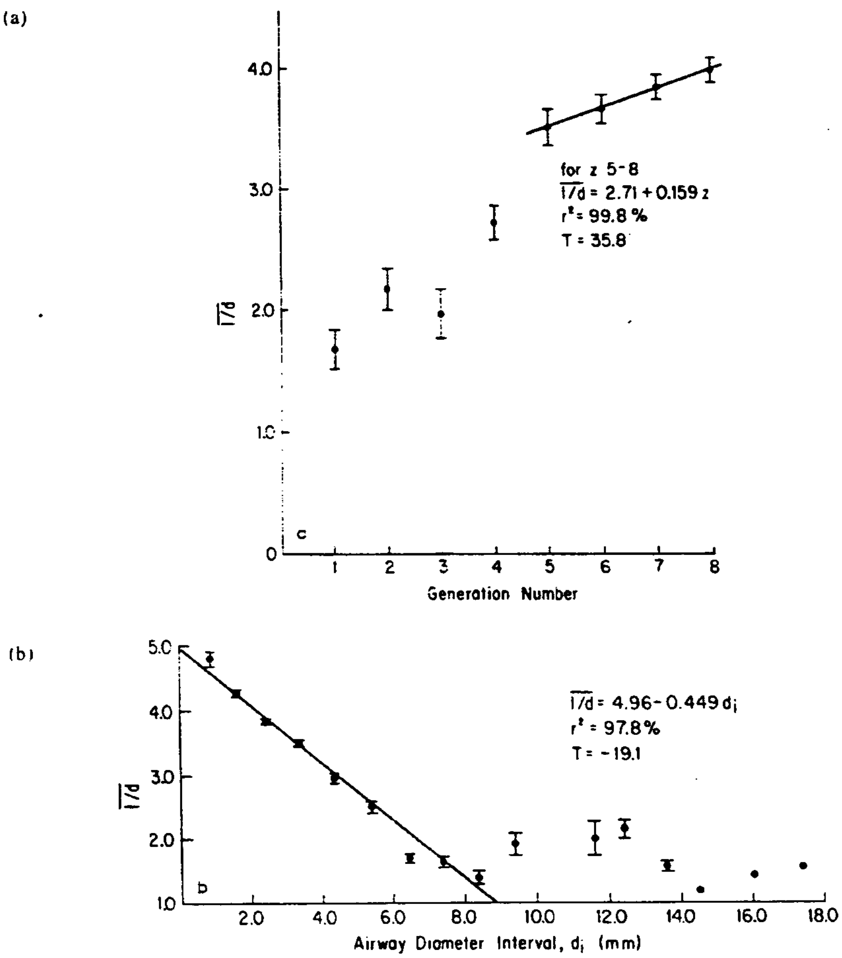

Fig. 3. (a) Average airway length to diameter ratios (mean ± SEM) *vs* generation. (b) Average airway length to diameter ratios (mean ± SEM) *vs* airway diameter intervals (d_i).

TABLE 2

Regression parameters for interrelationships of airway diameter, length and angle, based on the mean values for each cast and generation (n = 62)

Regression	m	b	r^2	s
ln length *vs* ln diameter	0.51	1.73	0.77	0.173
Angle *vs* ln diameter	10.1	12.2	0.36	8.175
Angle *vs* ln length	17.6	−16.4	0.37	8.123

share a common slope until $d_i \approx 9$ mm. This common slope region primarily represents airways of generations 5–8, which also showed a common slope in fig. 3a.

Best fit linear regressions of diameter, length, and angle based on mean values of each generation for each cast yielded the equations represented in table 2. Natural logs of diameter and length were used for the regressions since it was shown earlier (fig. 1) that these functions are a better description than the normal distribution functions. Inspection of table 2 reveals that the ln length *vs* ln diameter relationship is much stronger than branching angle *vs* either ln length or ln diameter. T ratio statistics of the slopes were significant at $P < 0.001$.

Analysis of variance was performed to examine the degrees of variability of dimensions in each generation between the eight casts (table 3). The degrees of variability of length within each individual and between individuals were approximately equal. On the other hand, for diameters, starting with the 4th and continuing through the 8th generation, there were significant differences between individuals. As intraindividual variability decreased, the interindividual differences remained relatively constant. For branching angles, significant differences between individuals appear in generations 7 and 8.

TABLE 3

Variability between eight casts by generation as determined by ANOVA

Generation	Length *F*-ratio	Diameter *F*-ratio	Angle *F*-ratio
2	0.06	1.45	0.03
3	1.06	1.37	1.23
4	2.35	2.79[a]	0.78
5	1.61	2.86[b]	1.92
6	2.00	3.34[c]	2.18
7	1.76	5.31[e]	4.71[c]
8	1.11	3.72[d]	4.26[e]

[a] Significant at $P \le 0.05$.
[b] $P \le 0.02$.
[c] $P \le 0.005$.
[d] $P \le 0.002$.
[e] $P \le 0.001$.

Discussion

The measurement of several human right lung casts in this laboratory has allowed estimation of the degree of variability in a population of young adult males. The mean morphometric values obtained from the eight casts were in close agreement with, but generally somewhat larger than, those of Weibel's Model A (1963), the most commonly used model (table 4). Comparison with the more recent model of Yeh and Schum (1980) revealed both airway lengths and branching angles to be in good agreement, although the Yeh and Schum values were generally smaller. On the other hand, the diameters in the Yeh and Schum model were consistently and, in most generations, considerably larger than those in our study.

An apparent discrepancy between both of the models and our data occurred in the lengths of generation 1 airways. This, however, is explained by the fact that the dimension of the Weibel as well as the Yeh and Schum first generation were the averages of the right and left major bronchi, and our measurements were of only the right. Since the left major bronchus is typically about twice as long as the right (Horsfield *et al.*, 1971; Jesseph and Merendino, 1957; Schlesinger *et al.*, 1977; Yeh and Schum, 1980), the ratio observed would be expected to be greater than 1.5. In contrast, the dimensions of more distal bronchi in the right and left lungs become much more similar. In this region, therefore, dimensions measured in right lungs are representative of both lungs.

Any comparison with other models must take into account the relative inflation of the fixed lungs. Weibel indicated that his measurements are based on "3/4 total lung capacity" as determined by the predicted and actual volume to weight ratio of the fresh

TABLE 4
Comparison of Weibel model A and Yeh and Schum typical path model to mean values of eight casts by generation

Generation	W/C[a]		Y – S·C[b]		
	Length	Diameter	Length	Diameter	Angle
0[c]	–	0.94	–	1.05	–
1[d]	2.03	0.86	1.86	1.10	1.10
2	0.96	0.91	0.90	1.24	0.72
3	0.68	0.89	0.87	1.31	0.76
4	1.09	0.98	0.85	1.42	0.79
5	0.94	1.00	0.89	1.62	0.81
6	0.91	1.00	0.90	1.55	0.84
7	0.84	0.92	1.05	1.51	1.04
8[d]	0.74	0.82	1.00	1.42	1.26

[a] Ratio of Weibel mean to current data means.
[b] Ratio of Yeh and Schum means to current data means.
[c] n = 3.
[d] n = 7.

lung. The degree of inflation of the lung in the Yeh and Schum model is not stated; however, the *in situ* cast preparation technique used results in a volume which was most probably at functional residual capacity. The TLCs of the fixed lungs in this study were determined by subtraction of the calculated tissue volume from the total volume of the lungs, as determined by water displacement. These values were then compared to the *in vivo* predicted values based upon the subject's age and stature. It is difficult to be certain of the true fraction of the TLC at which the Weibel lung was fixed, since the age, sex and stature of the subject are not available to calculate a predicted TLC. Also, since the volume of the Yeh and Schum lung is not known, the percentage of predicted TLC cannot be calculated in this case either.

Comparison of fig. 3a with a similar plot by Weibel (1963) of $\overline{l/d}$ (designated as $\bar{\delta}$ by Weibel) *vs* generation number, (z), shows differences in two respects. First, Weibel found a value for $\bar{\delta}_z$ of 3.25 for generations 4–10. Our data indicate an average $\overline{l/d}_z$ ratio of 3.75 ± 0.21 in a comparable region. It is not clear whether these values differ significantly because of the absence of a statistic indicating variability for Weibel's data. Secondly, while Weibel found that the $\bar{\delta}_z$ was constant, our data indicate that the length to diameter ratio is increasing in magnitude up to generation 8.

If $\overline{l/d}$ are plotted by diameter at 1.0 mm intervals as in fig. 3b, and as reported by Weibel (1963) for 0.5 mm intervals, additional comparisons may be made. Weibel determined a $\bar{\delta}_d$ of 3.25, and a slope of zero for diameters from 1.0 to 4.5 mm. Our data are consistent, with $\overline{l/d} = 3.84 \pm 0.66$ in the same region, but the magnitude of the ratio increases as diameter class size decreases. In this case, however, $\bar{\delta}_d$ clearly is not significantly different from $\overline{l/d}$. In addition, our data show a linear relationship for $\overline{l/d}$ *vs* d_i up to a diameter of 9 mm. For larger diameters, $\overline{l/d}$ becomes highly variable. This, however, may be attributable to the smaller number of samples measured in this region.

Another approach for describing the variability between individuals in this study involved calculation of coefficients of variation for length, diameter and branching angle for each generation (table 5). These values confirm the previous observation that diameters were least variable, while the branching angles were most variable in inter-

TABLE 5
Coefficients of variation for eight casts by generation

Generation	Length (%)	Diameter (%)	Angle of branching (%)
1	18.9	13.6	9.6
2	52.5	20.4	76.5
3	45.5	32.1	63.9
4	35.2	29.2	96.3
5	41.9	34.1	80.6
6	53.8	33.7	95.8
7	51.4	34.7	93.8
8	49.9	37.7	104.1

subject comparisons. Table 5 further clarifies the results of the analysis of variance shown in table 3. For length, inter- and intrasubject variability are moderate, with the former being slightly greater than the latter. The intersubject variability of diameter is relatively low, but the within subject error is even smaller, which produces the significant differences seen in generations 4–8 (table 3). Branching angles, which are highly variable between individuals, are also very variable within individuals until generations 7 and 8, when they become more uniform.

Comparison of our experimental data with the statistical description of the human tracheobronchial tree of Soong *et al.* (1979) yields the following observations. First, we are in agreement that the distributions of lengths and diameters of the airways within each generation are log-normal. Second, the coefficients of variation for length and diameter (fig. 4) are generally close, *i.e.*, $\leqslant 15\%$ difference, but our experimental data generally show more variability in both cases. For length, the Soong *et al.* curve predicts coefficient of variation values that are smaller in the most proximal airways, equal in the middle airways, and then greater than the present data in distal airways. For diameter, the Soong *et al.* values are consistently lower than our data for generations 1–8. It is important to recognize that the statistics presented by Soong *et al.* are derived from use of Raabe's *et al.* (1976) measurements in two lungs and Jesseph and Merendino's (1957) measurements of trachea and main bronchi, with Weibel's Model A as the underlying average; our values are independent of this limitation being from a heterogenous sample of eight casts.

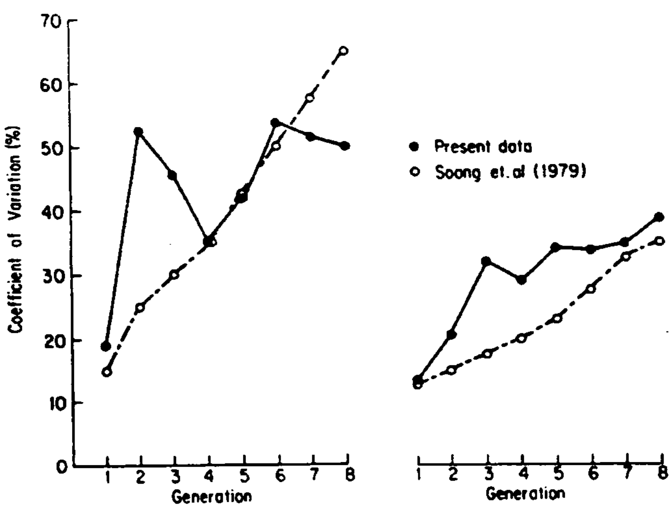

Fig. 4. Left: Coefficients of variation for lengths by generation number. Right: Coefficient of variation for diameters by generation number. (The Soong *et al.* curves are from data in table 2 of that paper.)

Conclusions. Morphometric measurements of generations 1–8 of the upper bronchial airways in casts of eight human right lungs have demonstrated that there is considerable variability in the lengths, diameters, and branching angles within the same generation. The intrasubject variability of dimensions decreases in airways distal to the trachea; on the other hand, intersubject differences in dimensions generally increase with increasing generation number. The length and diameter means of Weibel's Model A are in fairly good agreement, being within *ca.* 20% of those in the present study; however, the former are consistently smaller. The length and angle means of the Yeh and Schum model are in similar agreement with our study, but the mean diameters of the Yeh and Schum model are considerably larger. Weibel's model indicates an average length to diameter ratio which is constant for generations 4–10, and per diameter class. Current data indicate that $\overline{l/d}$ increases linearly for generations 5–8, and decreases linearly for diameter intervals from 1 to 9 mm. Airway lengths and diameters are closely related, even when generation to generation and interindividual differences are considered. However, branching angles are more variable, and cannot be predicted with as much confidence from length and diameter parameters.

There can be large differences in the dimensions of the upper airways between individuals and this should be taken into consideration when deposition and hazard evaluations for inhaled toxic substances are being considered.

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